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Treatment interruptions and duration associated with default among new patients with tuberculosis in six regions of Russia

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Summary
Objective: To determine the frequency and length of treatment interruptions among new pulmonary tuberculosis (TB) patients and to evaluate the duration of interruption associated with default in the tuberculosis services of six Russian regions.
Methods: This was a retrospective study of all adult patients with new pulmonary TB enrolled for treatment from April 1 to September 30, 2003. Data from patients with treatment outcomes of default (n = 84), failure (n = 130), death (n = 113), and success (n = 1444) were analyzed.
Results: The default rate was 4.6%. Treatment interruptions were frequent: 63% of patients who defaulted and 36% of those successfully treated had interruptions of treatment during the intensive phase, and 30% of those who defaulted and 45% of those with a successful outcome had interrupted treatment during the continuation phase. The length of treatment interruptions was 1—125 days during the intensive phase and 1—127 days during the continuation phase among patients with outcomes other than default. Patients with treatment gaps of 2—8 weeks during the intensive phase included 15.5% of defaulters, 13.9% of those with an outcome of failure, and 4.4% of those with treatment success. The integrated probability of default was ≥50% in those patients who missed at least 2—3 consecutive days of treatment during the intensive phase and at least one day during the continuation phase.
Conclusion: Treatment interruptions were frequent in TB patients in the six Russian regions. Interventions to improve treatment adherence in patients are necessary. Social support and incentive programs should be universally available for all patients from the start of the continuation phase of treatment, during the intensive phase for patients considered to be at

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risk for default, and for those patients who have missed at least 2–3 days of treatment during the intensive phase. Directly observed therapy (DOT) at home could be a recommendation for some patients.

Introduction

Tuberculosis (TB) has emerged as a serious public health problem in the Russian Federation since the dissolution of the Soviet Union in 1991.[1] The Russian Federation ranks twelfth among the 22 countries with the highest TB burden as defined by the World Health Organization (WHO).[2] In 2003, a study on a cohort of TB patients treated under the directly observed therapy short-course (DOTS) strategy in Russia showed only 61% of patients had a successful treatment outcome, while 7.8% of patients defaulted treatment, 12% had treatment failure, and 10% died.[2] These relatively poor results are primarily linked to the high prevalence of drug resistance, including multidrug-resistant (MDR)-TB.[2] Officially reported mean rates of MDR-TB for Russia range from 7.8–8.1% in new cases to 14.5–16.5% in previously treated cases;[3] however, MDR-TB rates in several settings are reported to be as high as 23% in new cases and 60% in previously treated cases.[4–6] The development of drug resistance is mainly attributed to: incomplete or inadequate treatment of patients with TB through weaknesses in TB control programs, inappropriate prescribing by providers, interruption of drug supply, failure to support patients on treatment, lack of infection control precautions, and poor compliance with treatment.[6,7]

Poor compliance to treatment is considered one of the most serious problems of TB control in the Russian Federation. The reported default rate in WHO-supported Russian regions, where case management is widely used (which includes DOT, coordination of ongoing care and services between inpatient and outpatient TB care providers, other clinical care providers, and social workers, referrals for psycho-social needs, patient education, and incentives for patients), is 3–20%, whilst in other regions, default rates may reach 30%.[3,8] Patients who default treatment are at increased risk for the development of drug resistance and relapse.[7] In addition to relatively high default rates in Russia, frequent shorter treatment interruptions have also been reported. For example, in 1999 in Ivanovo oblast, treatment interruptions lasting less than 2 months (2–8 weeks) occurred in 28% of smear-positive patients.[9] Shorter interruptions of treatment are also a point of concern, as non-compliance with treatment may lead to persistence and resurgence of TB, prolonged infectiousness, and increased transmission rates.[10,11] Non-adherent patients require longer periods of treatment and are less likely to complete treatment compared to patients who are compliant.[10,12]

This study was therefore designed to determine the frequency and length of treatment interruptions among new patients with pulmonary TB in Russia, and to evaluate the duration of treatment interruptions associated with the outcome of default. We aimed to develop practical recommendations on when it is necessary to start interventions for all patients identified as belonging to risk groups, in order to prevent default.

Methods

Study population

The study population included all patients with new pulmonary TB aged ≥16 years, who were enrolled for treatment on the Tuberculosis Register[13] from April 1 to September 30, 2003 in six Russian regions (Ivanovo, Orel, Vladimir, Belgorod, and Pskov oblasts, and the Republic of Chuvashia) (Table 1). All study regions are supported by the WHO and partners (International Federation of Red Cross and Red Crescent Societies and the US Centers for Disease Control and Prevention). The DOTS strategy of TB control was implemented in Ivanovo region beginning in 1995, in Orel in 1999, in Vladimir in 2000, and in the three other regions beginning in 2002. Social support programs for patients were in place in all six regions beginning in 1999–2003.[8] TB diagnosis was based on a bacteriologic confirmation by smear or culture. A clinical TB diagnosis was based on chest radiographic findings and clinical signs.[14] According to traditional Russian standards of care, the majority of patients received treatment in hospital during the intensive phase, while during the continuation phase the majority of patients were treated on an ambulatory basis under DOT on a daily basis or intermittently (3 times a week); however, for patients in our study this information was not collected. The WHO TB Control Programme in Russia determined the project to be a retrospective observational study, therefore ethical approval and informed consent from patients were not required.

Data collection and definitions

A standardized questionnaire was designed for data collection. Demographics, social history information, and microbiological laboratory results were abstracted from patient medical records. Information on treatment outcomes was obtained from the TB register.[13] Transferred patients were excluded from the study as information on treatment outcome was not available.

The frequencies and lengths of treatment interruptions during both phases of treatment were obtained from the 'TB treatment card'.[13] For each enrolled patient with a TB treatment card, we counted the total number of days of non-consecutive interruption (i.e., for how many days in total did the patient not receive TB medications during each phase of treatment), the maximum number of consecutive days of treatment interruption (i.e., the longest period during each phase of treatment when the patient did not receive TB medications; for defaulters this was the longest period of consecutive interruption before an interruption of ≥8 consecutive weeks), and the total number of interruptions (i.e., number of periods when the patient did not receive TB medications during each phase of treatment with the shortest possible period of not taking drugs equal to one day).

Table 1 Epidemiology of TB in the adult civilian population in six Russian regions, 2003[a].

Region	Total population of the region	Absolute number of registered new pulmonary TB cases	TB notification rate (number of new cases/100 000)	TB prevalence (number of cases/100 000)	TB mortality rate (number of TB deaths/100 000)
Orel	850 000	502	60.9	207.6	6.7
Ivanovo	1 129 800	695	64.0	188.9	18.8
Vladimir	1 503 700	1207	81.6	214.1	20.6
Chuvashia	1 305 000	926	72.9	262.4	15.6
Pskov	747 600	595	81.3	173.9	31.9
Belgorod	1 513 100	984	82.2	135.6	8.9

[a] Source: Analytical review of the situation with tuberculosis in the Russian Federation, 2004: characteristics of epidemiological process and TB services. Moscow, Russia: Ministry of Health and Social Development of the Russian Federation, Central Research Institute of Public Health and IT, and Research Institute of Phthisiopulmonology of the Sechenov Moscow Medical Academy; 2006 (in Russian).

The standard WHO definitions of patient categories and treatment outcomes were used.[14,15] The outcome of treatment default was defined as interruption of treatment for eight consecutive weeks or more.[14,15] Treatment interruption was defined as any interruption of treatment for at least one day, but for <8 consecutive weeks. A treatment gap was defined as a treatment interruption lasting ≥ 2 consecutive weeks and <8 consecutive weeks.[9]

Data analysis

Data were entered into a database using Microsoft Excel 2000 software (Microsoft Corp., Redmond, WA, USA). SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. Patient individual level data were analyzed. For continuous data, the two-sample *t*-test was used for normally distributed variables; otherwise the Wilcoxon non-parametric test was used. The Mantel–Haenszel Chi-square test was used to test for differences in proportions for categorical data; when the expected value of a cell was <5, Fisher's exact test was used instead. The Mantel–Haenszel odds ratio (OR) and corresponding 95% confidence interval (CI) was calculated for dichotomous variables. A *p*-value of ≤ 0.05 was defined as statistically significant.

The integrated probability of default was calculated by dividing the summary number of patients who defaulted treatment by each day of treatment, by the total number of patients who defaulted treatment ($N = 84$). Then integrated probability of default was calculated for the number of days of non-consecutive interruption and for the maximum number of consecutive days of treatment interruption (for the intensive and continuation phases of treatment). We found and reported cut-off points in the number of days of interruption (non-consecutive and maximum number of consecutive days) corresponding to $\geq 50\%$ and $\geq 75\%$ integrated probability of default.

Results

During the study period a total of 1805 pulmonary TB patients from the six regions were enrolled. The mean age of patients was 43 years (range 16–86); the majority (73%) were male. Fifty-seven percent of patients lived in a city, and 32% lived a distance of ≥ 5 km from their treatment site. Overall, 37% of patients were unemployed, 24% abused alcohol, 13% had a history of imprisonment, and 3% were homeless. Forty-six percent of patients were smear-positive. The treatment outcomes in the six regions were as follows: 1444 (80%) patients had successful or completed treatment, 84 (4.6%) patients defaulted, 130 (7.2%) patients had treatment failure, 113 (6.3%) died, and 34 (1.9%) were transferred. The default rate during the study period in the enrolled cohort of patients ($N = 1805$) was 2.3% ($n = 5$) in Orel, 2.8% ($n = 6$) in Ivanovo, 4.5% ($n = 17$) in Belgorod, 5.2% ($n = 20$) in Vladimir, 5.5% ($n = 15$) in Pskov, and 6.3% ($n = 21$) in Chuvashia. Among patients who defaulted treatment, default occurred during the intensive phase of treatment for 44% (37/84) of patients and during the continuation phase for 56% (47/84) of patients.

The frequency and length of treatment interruptions among pulmonary smear-positive and smear-negative TB patients are reported in Table 2. With regards to the subset of smear-positive patients ($N = 834$), defaulted patients had a significantly higher mean total number of days of non-consecutive interruptions during the intensive phase compared to patients with a successful treatment outcome (11.5 vs. 5.1 days), higher mean total number of interruptions (2.8 vs. 1.3), and longer mean maximum number of consecutive days of treatment interruption (6.9 vs. 2.7 days). Smear-positive patients who failed treatment had a significantly higher mean total number of days of non-consecutive interruptions during the intensive phase compared to patients with a successful treatment outcome (9.9 vs. 5.1 days), higher mean total number of interruptions (2.1 vs. 1.3), and longer mean maximum number of consecutive days of treatment interruption (5.0 vs. 2.7 days). No significant differences in frequency and length of treatment interruptions were found with regards to the continuation phase for smear-positive patients.

The association of treatment gaps (interruptions of 2–8 weeks) and default among pulmonary smear-positive and smear-negative TB patients for both phases of treatment is reported in Table 3. Similar results were obtained for the subset of smear-positive patients with default and with outcome of failure (data not shown).

The odds of treatment default among pulmonary smear-positive and smear-negative TB patients increased from 2.1 in patients who missed a total of 1–7 non-consecutive days of treatment during the intensive phase to 4.6 in patients who missed a total of >14 days of treatment (referent category 'no treatment interruptions') (Table 4). During the continuation

Table 2 Frequency and length of treatment interruptions among pulmonary smear-positive and smear-negative TB patients with treatment outcomes of success, default, failure, and death (N = 1771).

Treatment interruptions	Default (n = 84)			Failure (n = 130)			Death (n = 113)			Success (n = 1444)		
	Mean (95% CI)	Median	Range	Mean (95% CI)	Median	Range	Mean (95% CI)	Median	Range	Mean (95% CI)	Median	Range
Intensive phase												
Total number of days of non-consecutive interruptions	12.5[a] (7.9–17.1)	3.0	0–94	9.6[a] (6.6–12.7)	2.0	0–121	2.3[a] (0.8–3.7)	0	0–59	4.3 (3.7–4.9)	0	0–125
Total number of interruptions	2.6[a] (1.7–3.4)	1.0	0–24	2.4[a] (1.5–3.3)	1.0	0–46	0.5[a] (0.2–0.8)	0	0–11	1.1 (1.0–1.3)	0	0–33
Maximum number of consecutive days of interruption	7.6[a] (4.7–10.6)	2.0	0–57	4.9[a] (3.5–6.2)	1.0	0–38	1.7 (0.5–2.9)	0	0–58	2.3 (2.0–2.7)	0	0–57
Continuation phase												
Total number of days of non-consecutive interruptions	7.7 (2.9–12.4)	0	0–146	9.1 (5.7–12.5)	0	0–110	0.6[a] (0–1.5)	0	0–47	8.0 (7.2–8.8)	0	0–127
Total number of interruptions	1.7 (0.9–2.5)	0	0–17	1.6 (1.0–2.2)	0	0–20	0.1[a] (0–0.2)	0	0–6	2.0 (1.8–2.3)	0	0–31
Maximum number of consecutive days of interruption	2.4[a] (1.3–3.6)	0	0–27	3.9 (2.4–5.3)	0	0–52	0.5[a] (0–1.3)	0	0–47	3.7 (3.3–4.1)	0	0–57

[a] $p < 0.05$ for the mean in the two-tailed t-test in comparison to patients with a successful treatment outcome.

phase no positive association was found between total number of days of non-consecutive interruptions and default; missing a total of 1–7 or 8–14 non-consecutive days of treatment during the continuation phase was significantly less likely to have occurred among defaulters compared to those with a successful outcome (Table 4). Similar results were obtained for the analysis of the association of default with the maximum number of consecutive days of treatment interruption among pulmonary smear-positive and smear-negative TB patients (Table 5). A significant trend of increasing probability of default was found with an increasing total number of days of non-consecutive interruptions or maximum number of consecutive days of interruption during the intensive phase (both $p < 0.001$), while no significant trend was found for interruptions during the continuation phase ($p = 0.21$ and $p = 0.05$, respectively) (Tables 4 and 5).

The integrated probability of default based on the number of missed days of treatment is shown in Table 6.

Discussion

We found a relatively low default rate of 4.6% in the six Russian regions (compared to up to 30% in other regions according to the Russian Ministry of Health reports).[3,8] However, treatment interruptions were common: 63% of defaulted and 36% of successfully treated patients had interruptions of treatment during the intensive phase, and 30% of defaulted and 45% of patients with successful treatment outcomes had interrupted treatment during the continuation phase. The length of treatment interruptions was 1–125 days during the intensive phase and 1–127 days during the continuation phase without registering a default outcome, since these treatment interruptions occurred in a non-consecutive fashion (treatment was not interrupted for eight consecutive weeks or more), and accordingly to standard WHO definitions[15] and the Russian Order[14] such patients cannot be registered as having a default outcome. The integrated probability of default was ≥50% in those patients who missed at least 2–3 consecutive days of treatment during the intensive phase, and at least one day of treatment during the continuation phase.

A higher proportion of patients defaulted during the continuation phase than during the intensive phase of treatment. Historically the Russian TB control system has anticipated lengthy and frequent hospitalizations for TB patients.[16,17] Current regulations do not have specific standards or criteria for hospitalizations.[14] At present the mean duration of hospital stay in Russia is 86–90 days per admission following the traditional approach to treating TB patients in the hospital.[18] In the six DOTS regions where the study was conducted, the majority of patients received treatment in the hospital during the intensive phase, while the majority were treated as outpatients at TB services during the continuation phase; thus, direct observation of treatment was more easily ensured when a patient was hospitalized. This may explain our findings of strong associations of treatment default with higher total number of days of non-consecutive interruptions, higher total number of interruptions, and longer maximum number of consecutive days of interruption during the intensive phase, while any interruptions during the continuation phase were not predictive of default. Similar to our findings, Santha

Table 3 Treatment gaps (interruptions of 2—8 weeks) among pulmonary smear-positive and smear-negative TB patients with treatment outcomes of success, default, and failure ($N = 1658$).

Treatment interruptions for a consecutive 2—8 weeks	Success ($n = 1444$) *n* (%)	Default ($n = 84$)			Failure ($n = 130$)		
		n (%)	OR (95% CI)[a]	*p*-Value[a]	*n* (%)	OR (95% CI)[a]	*p*-Value[a]
During intensive phase	63 (4.4)	13 (15.5)	4.0 (2.1—7.6)	<0.001	18 (13.9)	3.5 (2.0—6.3)	<0.001
During continuation phase	119 (8.2)	5 (6.0)	0.7 (0.3—1.8)	0.68[b]	13 (10)	1.2 (0.7—2.3)	0.49
During both phases	11 (0.8)	0 (0)	-	1.00[b]	6 (4.6)	6.3 (2.3—17.3)	<0.001

[a] OR and *p*-values for comparison to patients with success as the treatment outcome.
[b] Fisher's exact test.

Table 4 Odds of treatment default for TB patients based on the number of total days of non-consecutive treatment interruptions among pulmonary smear-positive and smear-negative TB patients ($N = 1528$).

Total days of non-consecutive interruptions	Default ($n = 84$) *n* (%)	Success ($n = 1444$) *n* (%)	OR (95% CI)	*p*-Value
Interruptions during the intensive phase[a]				
0	31 (36.9)	928 (64.3)	1.0	
1—7	21 (25)	301 (20.8)	2.1 (1.2—3.7)	0.01
8—14	14 (16.7)	98 (6.8)	4.3 (2.2—8.3)	<0.001
>14	18 (21.4)	117 (8.1)	4.6 (2.5—8.5)	<0.001
Interruptions during the continuation phase[b]				
0	59 (70.2)	793 (54.9)	1.0	
1—7	9 (10.7)	251 (17.4)	0.5 (0.2—1.0)	0.04
8—14	3 (3.6)	130 (9.0)	0.3 (0.1—1.0)	0.04[c]
>14	13 (15.5)	270 (18.7)	0.7 (0.4—1.2)	0.16

[a] Cochran—Armitage trend test, two-sided, $p < 0.001$.
[b] Cochran—Armitage trend test, two-sided, $p = 0.21$.
[c] Fisher's exact test.

et al.[19] found that a higher likelihood of default was associated with irregularity in treatment during the intensive phase. In a study by Chang et al.,[20] poor, fair, or unknown initial adherence (i.e., adherence during the intensive phase) was found to be significantly associated with treatment default.

Treatment interruption did not contribute to an outcome of death, since patients who died had significantly shorter

Table 5 Odds of treatment default for TB patients based on maximum number of consecutive days of treatment interruptions among pulmonary smear-positive and smear-negative TB patients ($N = 1525$).

Maximum number of consecutive days of interruption	Default ($n = 84$) *n* (%)	Success ($n = 1441$) *n* (%)	OR (95% CI)	*p*-Value
Interruptions during intensive phase[a]				
0	31 (36.9)	930 (64.5)	1.0	
1—7	35 (41.7)	394 (41.7)	2.7 (1.6—4.4)	<0.001
8—14	5 (6.0)	59 (4.1)	2.5 (0.9—6.8)	0.07[c]
>14	13 (15.4)	58 (4.0)	6.7 (3.3—13.5)	<0.001
Interruptions during continuation phase[b,d]				
0	58 (69.9)	793 (55.2)	1.0	
1—7	14 (16.9)	418 (29.1)	0.5 (0.3—0.8)	0.009
8—14	7 (8.4)	113 (7.9)	0.9 (0.4—1.9)	0.69
>14	4 (4.8)	112 (7.8)	0.5 (0.2—1.4)	0.22[c]

[a] Cochran-Armitage trend test, two-sided, $p < 0.001$.
[b] Cochran-Armitage trend test, two-sided, $p = 0.05$.
[c] Fisher's exact test.
[d] Data were available for 83 defaulted patients, and 1436 patients with successful treatment.

Table 6 Integrated probability of default based on days of treatment interruptions among pulmonary smear-positive and smear-negative TB patients with default outcome ($N = 84$).

Integrated probability of default	Intensive phase		Continuation phase	
	Total number of days of non-consecutive interruption	Maximum number of consecutive days of treatment interruption	Total number of days of non-consecutive interruption	Maximum number of consecutive days of treatment interruption
≥50%	≥3	≥2	≥1	≥1
≥75%	≥11	≥6	≥3	≥2

and fewer interruptions during both the intensive and continuation phases compared to patients with a successful outcome. Previous studies from two Russian regions have found the survival time after TB diagnosis to be short (35—40 days) in those who die.[21,22] Major risk factors for an outcome of death in Russia include markers of advanced TB disease as a result of delayed diagnosis.[21,22] Therefore, factors other than treatment interruptions are likely to be associated with increased TB mortality in Russia. Findings in other studies have been controversial: several studies have demonstrated that death as an outcome is not associated with non-compliance[10] and irregular treatment,[19] while a study conducted in India showed that irregular or inadequate chemotherapy resulted in a four-fold increase in mortality.[23]

Based on our study results, the following practical recommendations can be made. When a patient interrupts treatment for a total of three or more non-consecutive days, or two or more consecutive days during the intensive phase, healthcare workers should promptly intervene and all measures should be taken to secure compliance, since the probability of default increases proportionally with an increasing number of days of interruption. These patients should be traced by telephone call or visit to their homes to identify reasons for non-adherence. Interventions for improving adherence should include: identification of patients who are at high risk for default at the very beginning of treatment, psychological counseling of patients and health education, social support, and incentives to keep patients on treatment. Social support and incentive programs should be universally available for all patients starting from the first day of the continuation phase of treatment. DOT at home could be a recommendation for some patients.

Conclusions

In summary, treatment interruptions were common in TB patients in six Russian regions, and treatment interruptions could be lengthy even in patients without an outcome of default. Social support and incentive programs should be universally available for all patients from the start of the continuation phase of treatment, during the intensive phase for patients considered to be at risk for default (such as the unemployed, alcohol abusers, and the homeless),[6] and for those patients who have missed at least 2—3 days of treatment during the intensive phase. All measures should be undertaken to keep patients on treatment.

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